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Measures of CNS-Autonomic Interaction and Responsiveness in Disorder of Consciousness

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Neuroimaging studies have demonstrated functional interactions between autonomic (ANS) and brain (CNS) structures involved in higher brain functions, including attention and conscious processes. These interactions have been described by the Central Autonomic Network (CAN), a concept model based on the brain-heart two-way integrated interaction. Heart rate variability (HRV) measures proved reliable as non-invasive descriptors of the ANS-CNS function setup and are thought to reflect higher brain functions. Autonomic function, ANS-mediated responsiveness and the ANS-CNS interaction qualify as possible independent indicators for clinical functional assessment and prognosis in Disorders of Consciousness (DoC). HRV has proved helpful to investigate residual responsiveness in DoC and predict clinical recovery. Variability due to internal (e.g., homeostatic and circadian processes) and environmental factors remains a key independent variable and systematic research with this regard is warranted. The interest in bidirectional ANS-CNS interactions in a variety of physiopathological conditions is growing, however, these interactions have not been extensively investigated in DoC. In this brief review we illustrate the potentiality of brain-heart investigation by means of HRV analysis in assessing patients with DoC. The authors' opinion is that this easy, inexpensive and non-invasive approach may provide useful information in the clinical assessment of this challenging patient population.

Keywords: central autonomic network, autonomic nervous system, disorders of consciousness, unresponsive wakefulness syndrome, heart rate variability

INTRODUCTION

Clinical evidence and neuroimaging research have documented retained modular brain activation and responsiveness in patients with Disorder of Consciousness (DoC) following brain injury even in the absence of integrated large-network processes known to sustain consciousness (Laureys et al., 2002; Bekinschtein et al., 2004, 2011; Owen et al., 2006; Monti, 2012; Naro et al., 2015; **Box 1**). In this respect, residual responsiveness in DoC appears to be mediated by varying network interactions (Riganello et al., 2013, 2015c; Crone et al., 2017; Duclos et al., 2017). Activation restricted to lower-level primary sensory cortices without involvement of higher-order associative

BOX 1 | Brain injury can result in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) characterized by arousal and spontaneous eye-opening in the absence of any sign of awareness, finalized action or communication. Levels of residual responsiveness define the Minimally Conscious State (MCS) (Giardino et al., 2004). A 2006 provocative report presented the case of a VS/UWS subject able to engage in mental tasks as indicated by her fMRI patterns of brain activations (Owen et al., 2006). Levels of responsiveness involving higher brain functions have been observed in subjects otherwise classified as VS/UWS according to clinical criteria (Laureys et al., 2007; Boly et al., 2008; Bruno et al., 2010; Owen, 2014; Pistoia et al., 2016; Riganello et al., 2018b). These observations were mostly based on regional brain activation in response to stimulus conditions in controlled setups; stimulus-related functional changes in the autonomic nervous system (ANS) function have also been described. Still highly debated, e.g., in subjects in a VS/UWS, these observations challenge the current definitions and our understanding of both responsiveness and consciousness, with an impact on the clinical decision-making process (Laureys et al., 2010; Riganello et al., 2016, 2018a,b). The extent to which regional brain activations can be considered equivalent to, or compatible with behavioral responses in indicating (residual or covert) consciousness remains controversial and the current standards by which patients surviving severe brain injury should be regarded as being conscious or unconscious have been questioned (Celesia, 2013; Celesia and Sannita, 2013). In this respect, scientific research has introduced novel criteria of evaluation not yet fully integrated in the current nosography of disorders of consciousness (DoC), which is now undergoing a tacit, but not uncontroversial, revision (Monti and Sannita, 2016).

cortices has been described in vegetative state/unresponsive wakefulness syndrome (VS/UWS) (Soddu et al., 2015; Marino et al., 2017). Partially preserved activation in higher-order associative cortices has been demonstrated in Minimally Conscious State (MCS) (Di Perri et al., 2013, 2016; Demertzi et al., 2015), whereas restoration of thalamocortical connectivity has shown to relate to consciousness recovery (Laureys et al., 2000; Monti et al., 2014). A large amount of research by means of neuroimaging techniques has revealed that several aspects of relatively high-level functions, including sensory and linguistic processing and learning dynamics, can survive and remain operative in DoC (Aubinet C- HBM 2018, Laureys et al., 2007; Boly et al., 2008; Majerus et al., 2009; Bruno et al., 2010).

Neuroimaging studies have further shown functional interaction between autonomic nervous structures [i.e., the parasympathetic and sympathetic branch of the Autonomic Nervous System (ANS)] and the neuronal networks involved in higher brain functions, including attention and conscious processes (Napadow et al., 2008; Thayer et al., 2012; Ruiz Vargas et al., 2016; Valenza et al., 2017). Heart Rate Variability (HRV), that is the physiological phenomenon of variation in the time interval between consecutive heartbeats, is thought to reflect the complex interaction between brain and cardiovascular system (Thayer and Lane, 2009; Ernst, 2017). HRV entropy, a measure of the complexity of HRV, has shown to discriminate VS/UWS and MCS patients and was found to correlate with the ANS functional status (Riganello et al., 2018b).

In agreement with this line of observation, indices of ANS functions have proved reliable in detecting responsiveness and predicting recovery following neuro-rehabilitation in VS/UWS (Wijnen et al., 2006; Riganello et al., 2015a). There is growing evidence that ANS function can be monitored non-invasively

and neuroimaging studies have provided evidence of the two-way interplay between heart and brain. As a result, interest in the bidirectional ANS-CNS interaction in a variety of physiopathological conditions is growing (de Morree et al., 2013; Riganello et al., 2014; Bassi and Bozzali, 2015; Chen et al., 2017; Doehner et al., 2018), however, the ANS-CNS interaction in DoC has so far not been extensively investigated.

ANS-CNS INTERACTION IN DOC

A concept model Central Autonomic Network (CAN) (Benarroch, 2007b) has been proposed to describe the ANS-CNS two-way interaction and the continuous modulation of homeostatic processes and allostatic adaptation to internal or external requirements (Friedman, 2007; Thayer et al., 2012; Riganello, 2016). Its functional organization involves the forebrain (anterior cingulate, nucleus accumbens, insula, ventromedial prefrontal cortex, amygdala, and hypothalamus with bidirectional interactions between rostral and caudal systems), brainstem (periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, and the reticular formation of ventrolateral medulla). At spinal level it operates via neuronal projections of segmental reflexive ANS control (**Figure 1**). These structures receive converging visceral and nociceptive inputs (including those from thermo- and muscle receptors) and generate stimulus-specific patterns of autonomic response via projections to preganglionic sympathetic and parasympathetic neurons (Saper, 2002; Benarroch, 2007a). The forebrain and brainstem are involved in the modulation of autonomic output in response to pain and to emotional, behavioral, or “cognitive” stimuli (Hagemann et al., 2003; Berntson and Cacioppo, 2004; Thayer and Sternberg, 2006; Friedman, 2007; Thayer and Lane, 2009; Riganello et al., 2012a).

HEART RATE VARIABILITY AND HEART/BRAIN INTERPLAY

HRV measures (i.e., variables analyzed in time domain, frequency domain and non-linear measurements) describe the ANS functional setup, and are thought to reflect higher brain functions - at least to some extent - and to qualify as independent indicators of CNS-ANS interaction (Napadow et al., 2008; Thayer and Lane, 2009; Thayer et al., 2012; Tonhajzerova et al., 2012) (**Box 2** and **Table 1**). HRV measures reflect the activity of physiological factors modulating the heart rhythm and its adaptation to changing conditions (Carney et al., 2005; Garan, 2009; Shaffer et al., 2014). The vagus nerve is the major channel involved in the afferent neurological signals relayed from the heart and other visceral organs to the brain, including the baroreflex signals (de Lartigue, 2014). Brain morphological variants in the right striatal and limbic structures involved in the ANS functional organization were found to associate with differences in cardiac vagal function (Thayer and Lane, 2000; Napadow et al., 2008; Critchley, 2009; Lane et al., 2009) and to significantly contribute in the information flow in all frequency

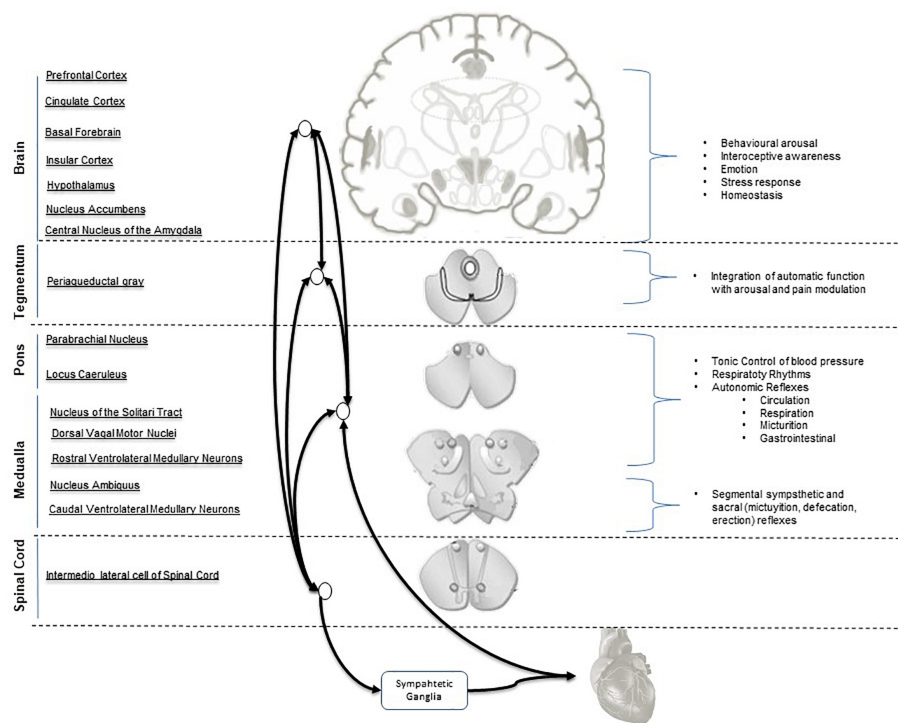


FIGURE 1 | Central Autonomic Network (CAN) hierarchical organization and interconnections. Parasympathetic output is mediated mainly by the nucleus of the vagus and nucleus ambiguus. Sympathetic output is mainly mediated by the intermediolateral column cell.

bands during sleep (Faes et al., 2014). In the absence of cardiac disorders, stimulus- or condition-related HRV changes are in the range of physiological variability and require processing in the time and frequency domains or by geometrical or non-linear methods to be identified (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Rajendra Acharya et al., 2006). HRV methodologies benefit from being easy to record, inexpensive and non-invasive as compared to neuroimaging techniques. HRV measures are obtained from a signal (the heart tachogram) with excellent signal-to-noise ratio; procedures for sophisticated data analyses are usable without substantial loss in information (Nait-Ali, 2009). HRV is easier to apply than alternative techniques for ANS investigation (cardiac norepinephrine spillover, microneurographic techniques, or direct recording from skeletal muscle) (Berne et al., 1992; Esler, 1993; Wallin and Charkoudian, 2007). It is particularly applicable in studies on large subject samples or under experimental conditions where accurate laboratory procedures are not possible, such as in case of limited/null collaboration (e.g., in intensive/semi-intensive care units or in DoC) (Mowery et al., 2008; Norris et al., 2008a,b; Ryan et al., 2011).

HRV AND DOC

HRV is a possible index of consciousness attention (Babo-Rebello et al., 2016; Cobos et al., 2019) and emotional states

(Shi et al., 2017) in healthy subjects. The interaction between consciousness, attention and HRV has been documented in patients with DoC. VS/UWS and MCS subjects were more likely to respond to standard visual and auditory stimuli when the HRV normalized unit of LF (nuLF) ranged between 10–70 and LF peaked around 0.1 Hz (Riganello et al., 2013), thus suggesting a functional relationship between responsiveness and the sympatho-vagal balance; a correlation between HRV parameters and improvement of consciousness has been documented, and higher value of nuLF associated to a better outcome in VS/UWS patients (Riganello et al., 2015a; Wijnen et al., 2006).

In frequency domain, HRV total power (TP) as well as LF and HF power were found significantly decreased in patients with Glasgow Coma Outcome Extended (GOSE) (Weir et al., 2012) score <5 (Hendén et al., 2014).

A correlation between HRV entropy (index of the brain-heart interaction complexity) and brain activation has been also described. Approximate Entropy (ApEn) values were lower in VS/UWS patients than in healthy control whereas no differences were found for all linear parameters [Root Mean Square of Successive Differences between normal heartbeats (RMSSD), Standard Deviation of RR peak (SDRR)] (Sarà et al., 2008). We have recently found lower Multiscale Entropy (MSE) values in VS/UWS than in MCS, which correlated with the Coma Recovery Scale (CSR-R) total score. A functional connectivity pattern involving the CAN system has been documented, thus proposing HRV entropy as an indirect tool to measure and monitor connectivity changes in this neural

BOX 2 | HRV – Heart rate variability is defined as the R-R interval fluctuation of normal sinus beats around its average value. HRV is analyzed in time domain, frequency domain and by non-linear methods both in short (usually 5 min) and long-time recordings (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). ANS functional contributions can be differentiated by analyses in the frequency domain, usually in three frequency band: High Frequency (HF) (0.15–0.5 Hz), Low Frequency (LF) (0.04–0.15 Hz), and (VLF) Very Low Frequency band (0.0033–0.04). The power, relative power and peak of each frequency band, the normalized value of HF (nuHF) and LF (nuLF) and the ratio between HF and LF (LF/HF) are the parameters usually considered. HF reflects parasympathetic activity as the HR variations related to the respiratory cycle. LF (0.04–0.15 Hz) mainly reflects baroreceptor activity during resting conditions and is known also as “baroreceptor range” (Malliani, 1995); it reflects contributions from both the parasympathetic and sympathetic systems and blood pressure regulation via baroreceptors and the baroreceptor activity in resting conditions (Malliani, 1995; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Berntson et al., 2007; Lehrer, 2007). The parasympathetic system affects heart rhythms down to 0.05 Hz, while the sympathetic system does not seem to generate rhythms above ~0.1 Hz. In humans, the delay in the feedback loops of baroreflex system have distinctive high-amplitude peak in the HRV power spectrum around 0.1 Hz (Vaschillo et al., 2011; Lehrer and Eddie, 2013) due to the feedback loops between heart and brain (deBoer et al., 1987; Baselli et al., 1994). There is some evidence for an association between VLF band (0.0033–0.04 Hz) and all-cause mortality (Shaffer et al., 2014), however, the physiological mechanisms responsible for activity within this band are not clear although probably related to thermoregulation, the renin-angiotensin system, and other hormonal factors (Akselrod et al., 1981; Cerutti, 1995; Claydon and Krassioukov, 2008). The LF/HF ratio has controversial interpretations, with the LF power possibly generated by the sympathetic, the HF power by the parasympathetic system and their ratio indicating both parasympathetic or sympathetic dominance (Pagani et al., 1984; Montano et al., 1994). HRV descriptors are also derivable by non-linear methods. Development in the non-linear theories provides new instruments to analyse the entropy domain [such as the simple or approximate entropy (ApEn)], better describe the complexity, irregularity or randomness of HRV and its changes, the non-linear temporal relationships with other metrics such as functional connectivity, and extract information about the complexity of the two way brain-heart interaction (Norris et al., 2006; Ryan et al., 2011; Shaffer et al., 2014; Riganello et al., 2018b).

system (Riganello et al., 2018b). In a Evoked Response Potential (ERP) study based on nociceptive repeated laser stimulation MCS showed partially preserved cortical activations, higher ERP γ -power magnitude and Standard Deviation of Normal-to-Normal intervals (SDNN) compared to VS/UWS patients (Calabrò et al., 2017). Other studies on nociceptive stimulation documented a correlation between the level of consciousness and HRV-entropy (Riganello et al., 2018a; Tobaldini et al., 2018), with lower values of entropy detected in VS/UWS than in MCS patients or in healthy subjects, and correlated to the CRS-R total scores (Riganello et al., 2018a). The above results indicate a decrease of complexity in the modulation of the response to noxious stimuli in VS/UWS subjects and a less complex ANS modulation in the two way brain-heart interaction compared to MCS.

Similar results have been observed in response to complex (musical) stimuli. Music interventions were associated with favorable behavioral and physiological responses in several studies, however, methodological quality and outcomes were heterogeneous (Grimm and Kreutz, 2018). After 14-day of

music stimulation SDNN and RMSSD of VS/UWS patients increased, indicating the activity of the cardiovascular system was enhanced (Lee et al., 2011). Contrasting observations were found in the direction of the RMSSD values in a work on MCS and VS/UWS patient, who were presented live preferred music and live improvised music (O’Kelly and Magee, 2013). A significant decrease in entropy was observed in VS/UWS subjects listening to four musical pieces of different structural complexity, whereas no differences between the same selected musical pieces were observed in healthy controls under comparable experimental conditions (Riganello et al., 2015b). The quality (positive or negative) of the emotional responses was correlated to extreme (low or high) nuLF values (Riganello et al., 2010). Higher values in both time and frequency domain were observed during affective than during non-affective auditory stimulation in VS/UWS patients suggesting the possibility to discriminate between different stimuli (Machado et al., 2007; Gutiérrez et al., 2010).

The clinical and scientific evidence suggests a diagnostic and prognostic relevance of HRV parameters in DoC of different aetiologies (e.g., traumatic brain injury (TBI), haemorrhagic, and anoxic) (Keren et al., 2005; King et al., 2009; Ryan et al., 2011; Almeida et al., 2017). Decreased values in the different domains of HRV analysis has been associated with worsened health condition. HRV parameters extracted in the time domain (SDNN, SDNN index, and RMSSD) were also found decreased after TBI in the absence of major DoC (Rapenne et al., 2001; DeGiorgio et al., 2010; Kim et al., 2017) and associated to clinical worsening and to mortality in the acute phase (Morris et al., 2006; Norris et al., 2006; Mowery et al., 2008; King et al., 2009). In children, suppression of LF and HF bands of the power spectrum were associated with brain death and poor outcome (Goldstein et al., 1993, 1998) and decreases in LF/HF was correlated with increases in intracranial pressure and mortality (Biswas et al., 2000). In TBI adults, decreased LF, HF, LF/HF, and TP were associated with brain death, increased mortality, increased intracranial pressure, and poor outcome (Winchell and Hoyt, 1997; Rapenne et al., 2001; Papaioannou et al., 2006). Reduced HRV complexity has proved to be an independent predictor of mortality (Batchinsky et al., 2007). Decreased ApEn values have been associated to increased mortality in acute TBI (Papaioannou et al., 2008; Gao et al., 2016) and the MSE was found to identify trauma patients at risk of in-hospital death, and predicts mortality independent of probability of survival based on location and mechanism of injury (Norris et al., 2008a,b).

COMMENT AND PERSPECTIVES

The CAN model of ANS-CNS functional interaction is helpful to describe the phenomena underlying residual responsiveness in DoC within the framework of homeostatic and allostatic organization, at least in part and to a degree of pathophysiological approximation (Friedman, 2007; Shen et al., 2016; Thome et al., 2017). The suitability of HRV analysis in detecting residual (covert) brain function in DoC has been documented (Wijnen et al., 2006; Gutiérrez et al., 2010; Riganello, 2016;

TABLE 1 | Most common measures used in HRV analysis.

	Parameter	Unit	Description	
Time domain	SDNN/SDRR	ms	Standard deviation of NN/RR intervals	In the time domain both sympathetic and parasympathetic nervous systems contribute to SDNN. Differently from “RR,” “NN” means that abnormal beats, like ectopic beats, have been removed. RMSSD is used to estimate the vagally mediated changes reflected in HRV. It is strongly correlated with pNN50
	SDANN		Standard deviation of the average normal-to-normal (NN) intervals for each of the 5 min segments during a 24 h recording	
	SDNN index		Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24-h HRV recording	
	pNN50	%	Percentage of adjacent NN intervals that differ from each other by more than 50 ms (pNN50) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996)	
	RMSSD	ms	Root mean square of successive differences between normal heartbeats	
Frequency Domain	VLF, LF, and HF power	ms ²	Absolute power of total or of the single band of frequency calculated by FFT or Auto Regressive model	HF, LF and VLF bands of frequency are associated with several aspects of the ANS. The HF band reflects parasympathetic activity and corresponds to the HR variations related to the respiratory cycle. The LF band reflects contributions from both the parasympathetic and sympathetic systems. It mainly reflects baroreceptor activity during resting conditions. The sympathetic system is below 0.1 Hz. The VLF band is associated to thermoregulation, the renin-angiotensin system, and other hormonal factors, but also to the intrinsic heart activity. The normalized values (nuLF and nuHF) express the quantities on a more easily understood proportion (0–1) or percentage (0–100%) scale basis. The LF/HF ratio is generally used to represents the ratio of sympathetic to parasympathetic nerve activity, also if the LF is contaminated by the vagal system. nuLF, nuHF, as well as LF/HF ratio should be considered equivalent carriers of information with regard to sympathovagal balance (Burr, 2007)
	nuLF	nu	Relative power of the low-frequency band in normal unit	
	nuHF		Relative power of the high-frequency band in normal unit	
	LF/HF		Ratio LF-to-HF power	
	Peak VLF, LF, and HF	Hz	Peak of frequency of VLF, LF, or HF band	
Non-linear methods	Approximate entropy		Measures the regularity and complexity of a time series	The entropy reflects of the amount of irregularity in the R-to-R interval. Lower or higher values are index of higher or lower complex activity of the ANS. Further higher values were associated to a higher brain-heart two way interaction. The SampEn was introduced to counteract some shortcomings of the ApEn. The SampEn does not count a self-match of vectors, eliminating the bias toward regularity, and has been suggested to be independent of data length (Yentes et al., 2013)
	Sample entropy		Measures the regularity and complexity of a time series. Sample entropy can be calculated from a much shorter time series of fewer than 200 values	
	Multiscale entropy		Quantify the degree of irregularity over a range of time scales. The time series are constructed by averaging the IBI/tachogram's data points within non-overlapping windows of increasing length	

Garbarino and Sannita, 2015). Autonomic function, ANS-mediated responsiveness and the ANS-CNS interaction qualify as possible independent indicators for clinical functional assessment, diagnosis and prognosis in DoC (King et al., 2009; Ryan et al., 2011; Sannita, 2015; Riganello, 2016). In a reversed perspective, research on the residual modular functions in DoC can provide unique information about brain mechanisms/functions and ANS-CNS interplay that can be investigated in these patients under experimental conditions that are rigorously controlled (Monti, 2012; Riganello et al., 2012b; Sannita, 2014; Shen et al., 2016; Chennu et al., 2017; Kiryachkov et al., 2017).

Brain function is modulated by complex neural networks and non-neuronal factors which interact with each other, individually or collectively account for inter/intra-individual variability, and reflect/depend on the circadian rhythms and the wakefulness/sleep alternation (Bullock, 1970; Sannita, 2006; Garbarino et al., 2014, 2019; Soddu and Bassetti, 2017). The HRV concomitants of the major shift toward sympathetic activation associated to peak cortisol levels at the morning sleep-to-wake transition are an example in this regard (Bilan et al., 2005; Boudreau et al., 2011, 2012). HRV proved reliable in investigating the ANS-CNS functional interaction underlying residual responsiveness in VS/UWS or MCS subjects (Wijnen et al., 2006; Gutiérrez et al., 2010; Candelieri et al., 2011; Sannita, 2015; Riganello, 2016). CNS and ANS setups, however, change over time spontaneously or due to homeostatic or allostatic requirements with different timing and latencies. HRV measures at rest and in response to stimulus conditions have higher time resolution and reflect rapid changes better than clinical or neuroimaging markers of damage, with greater variability during the day (Bekinschtein et al., 2009; Candelieri et al., 2011; Riganello et al., 2013, 2015c; Abbate

et al., 2014; Sannita, 2015; Blume et al., 2017). Time appears to be a source of variability adding to the variety of environmental factors (light and noise in hospital settings, timing of medication or non-pharmacologic interventions, comorbidities, etc.) also needing consideration, both as co-determinants of the circadian rhythms (Soddu and Bassetti, 2017) and in view of the ANS major role in internal environment constancy and adaptation that are fundamental to homeostasis. Systematic investigation is still lacking and appears advisable.

AUTHOR CONTRIBUTIONS

FR, SKL, CDP, VP, WS, and SL have equally collaborate to this work with substantial, direct and intellectual contribute, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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